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MEMORANDUM

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This document is the revised human health risk assessment for reregistration of the herbicide, sodium acifluorfen and incorporates phase 3 public comments. Several minor changes were made to the product chemistry and occupational/residential chapters (see attached memos). The principal change to this risk assessment included a new Q_1^* value which resulted in new calculations for cancer risk.

Attached are memos for the Q_1^* , dietary exposure analysis, product chemistry chapter, occupational and residential exposure assessments and memos for responses to comments in the respective disciplinary chapters.

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1.0 EXECUTIVE SUMMARY

This document is the revised human health risk assessment for the reregistration of the herbicide, sodium acifluorfen and incorporates phase 3 public comments. This risk assessment includes a new Q_1^* [1.27×10^{-2} (mg/kg/day)⁻¹], new dietary and occupational/residential assessments, and new DWLOC values.

Sodium acifluorfen is a diphenyl ether used as a contact herbicide for selective pre- and post-emergence control of annual broad-leaf weeds and some grasses in rice, peanuts, and soybeans. Residential homeowners may use sodium acifluorfen products as a spot treatment weed killer.

Tolerances for plant and animal commodities are expressed in terms of the combined residues of sodium acifluorfen and the acid, methyl ester, and amino metabolites. It is recommended that livestock tolerances be revoked because there is no reasonable expectation of residues being transferred to livestock commodities via consumption of feed items derived from crops treated with sodium acifluorfen according to the current use directions. The residues of concern to be used for the assessment of drinking water exposure and dietary risk are acifluorfen and acifluorfen amine. Acifluorfen is also a metabolite/degradate of another herbicide, lactofen.

The toxicity database is adequate for selecting toxicity endpoints for risk assessments, although a developmental neurotoxicity study is required because of neurotoxicity which occurred in a developmental rat study (dilated lateral ventricles of the brain).

Sodium acifluorfen has low acute oral, dermal and inhalation toxicity, and is not a skin sensitizer, but caused severe eye and moderate skin irritation. Liver and kidney toxicity occurred in subchronic and chronic toxicity studies.

Acifluorfen produced a statistically significant increase in the incidence of liver tumors (adenomas and carcinomas) and stomach tumors (papillomas) in mice and is classified as a Group B2, probable human carcinogen. The Q_1^* is 1.27×10^{-2} (mg/kg/day)⁻¹. Acifluorfen was weakly recombinogenic in *Saccharomyces cerevisiae* when nonactivated and was weakly mutagenic in a bacterial reverse mutation assay when activated but was negative in three subsequent bacterial reverse mutation assays.

A developmental toxicity study in rats found qualitative evidence of increased susceptibility of offspring because developmental toxicity (increased resorptions, reduced fetal weights, slightly dilated lateral ventricles of the brain, hemorrhage in the eyeball, slight dilation of the renal pelvis, hemorrhage in peritoneal cavity and subcutaneous spaces, and changes in ossification) was accompanied by minimal maternal toxicity (excess salivation and piloerection). Increased resorptions occurred in a developmental toxicity study in rabbits. Toxicity in a 2-generation reproduction study in rats included increased pup mortality and kidney lesions; there were no changes in reproductive parameters.

The FQPA safety factor should be retained at 10x when assessing acute dietary and short/intermediate-

term residential (non-occupational) exposures for females 13-50. The 10x safety factor was retained for these exposure scenarios because there was a qualitative increase in susceptibility in the rat developmental study and there is a datagap for a developmental neurotoxicity study. The FQPA safety factor should be reduced to 3x when assessing chronic dietary and long-term residential (non-occupational) exposures for females 13-50 and infants and children subgroups. The safety factor was reduced to 3x because there is a data gap for the developmental neurotoxicity study. The qualitative increase in susceptibility seen after *in utero* exposure in the developmental rat study has no bearing on chronic exposure scenarios.

The acute population adjusted dose (aPAD) for dietary exposure for females 13-50 years of age is 0.02 mg/kg/day and is based upon decreased fetal body weights and an increased incidence of dilated lateral ventricles of the brain in a developmental rat study (NOAEL = 20 mg/kg/day). An aPAD was not selected for other population groups. The chronic PAD (cPAD) for the general population is 0.013 mg/kg/day based upon microscopic kidney lesions in both generations of a 2-generation reproduction study (NOAEL = 1.25 mg/kg/day). The chronic PAD for females 13-50, infants, or children is 0.004 mg/kg/day from the same study. The endpoint for short- or intermediate-term dermal or inhalation is the NOAEL of 20 mg/kg/day from the developmental rat study based upon decreased fetal body weights and an increased incidence of dilated lateral ventricles of the brain. The Q^*_1 for carcinogenic effects is $5.30 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$ based upon liver tumors and stomach tumors in a mouse carcinogenicity study.

A dietary exposure less than the acute or chronic population adjusted dose (PAD) is not considered to be of concern. **Calculated acute and chronic dietary exposures were all less than 1% of the PAD and were not of concern in a tier 3 analysis using anticipated residues and per cent crop treated data. For dietary carcinogenic risk, the Agency's level of concern is 1×10^{-6} . Calculated dietary exposure resulted in a lifetime risk of 5.2×10^{-9} which is less than the level of concern.**

Drinking water exposure to acifluorfen may occur due to use of the herbicide, sodium acifluorfen, or may be present as a degradate of the herbicide, lactofen. Acifluorfen was detected in several monitoring studies for water. Acifluorfen was detected in 56 out of 283 ground water samples with concentrations ranging from 1 to 46 : g/L. The overall mean for the 56 detections was 8.36 : g/L. The Pesticides in Ground Water Database (PGWDB, USEPA, 1992) reported residues in 4 of 1185 wells sampled with concentrations ranging from 0.003 to 0.025 : g/L. The only surface water monitoring for acifluorfen is that from the USGS National Water Quality Assessment (NAWQA). The NAWQA study reports a single acifluorfen detection of 0.17 : g/L out of 965 samples collected from major aquifers and 1 detection (0.07 : g/L) out of 314 samples collected from shallow urban ground water.

Drinking water levels of comparison (DWLOCs) were calculated for use as a surrogate measure of exposure because uncertainties in the water monitoring data precluded their use in quantitative risk assessments. The DWLOCs were compared to modeled concentrations of acifluorfen calculated by the Environmental Fate and Effects Division, using PRZM/EXAMS and SCI-GROW modeling

software.

The only scenario in which modeled water concentrations exceeded the DWLOC is for cancer risk: modeled concentrations for sodium acifluorfen in ground water (10.3 µg/l) and for acifluorfen as a lactofen degradate (5.4 µg/L) in ground water exceeded the DWLOC (2.8 µg/L). This means that there may be concerns for cancer risk by drinking water exposure and further water monitoring may be indicated for refining drinking water exposure estimates.

The margins of exposure (MOEs) for two occupational exposure scenarios (mixing/loading liquids for groundboom application and mixing/loading liquids for aerial application) are less than 100 at the baseline level of protection, and therefore exceed a level of concern. The MOEs for the remainder of the exposure scenarios are above 100 for baseline and higher levels of mitigation and therefore do not exceed HED's level of concern.

The calculations of private grower and professional acifluorfen applicators' cancer risks indicate that one scenario (mixing/load liquids for aerial application) exceeds 1.0×10^{-4} at the baseline level. There are no concerns for post-application exposure of workers to sodium acifluorfen.

There are no concerns for residential exposure to sodium acifluorfen, either for non-carcinogenic risk or for carcinogenic risk. There are no concerns for residential post-application exposure to sodium acifluorfen.

Short-term aggregate exposure for non-carcinogenic risk was determined not to be of concern. The DWLOCs for short-term aggregate exposure indicated that drinking water exposure for carcinogenic risk may be of concern. Intermediate- and long-term exposure to sodium acifluorfen are not expected to occur.

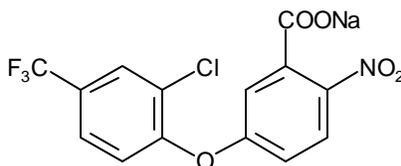
No incidents related to the use of sodium acifluorfen were reported from any of the data sources consulted by the Health Effects Division.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Sodium acifluorfen TGAI (-78% pure) is a light yellow powder with a melting point of 274-279° C (with decomposition), bulk density of 25.11 lb/ft³ (free fall) and 32.08 lb/ft³ (packed), octanol/water partition coefficient (P_{ow}) of 1.55 at pH 7, and vapor pressure of <1.33 x 10⁻⁵ Pa at 25° C. Sodium acifluorfen is soluble in water (62.07 g/100 mL), and most organic solvents (64.15 g/100 mL in methanol, 5.37 g/100 mL in octanol), and is practically insoluble (<5.0 x 10⁻⁵ g/100 mL) in hexane at 25 C°.

Common Name: Sodium Acifluorfen

Chemical Name: Sodium 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate)



3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

The toxicological database of acifluorfen was adequate for selection of toxicological endpoints for use in human risk assessments. However, the Hazard Identification Assessment Review Committee recommended that a developmental neurotoxicity study in rats be conducted based on neurotoxicity observed in a developmental toxicity study in rats (increased incidence of dilated lateral ventricles of the fetal brain, MRID 00122743). In addition, no neurotoxicity studies are available for acifluorfen or for structurally related compounds which might provide an understanding on the effects of acifluorfen on the developing nervous system.

Sodium acifluorfen is a diphenyl ether which is the active ingredient of the herbicide, Blazer. Toxicological data are available for Blazer and for another registration, Tackle, which was previously manufactured by another company. The data on Tackle are generally more current and acceptable. Discussions of the toxicology of acifluorfen are mainly based on data derived from the studies with Tackle, and where appropriate, the Blazer toxicity data are discussed. Tackle contained approximately 20% to 24% acifluorfen as the active ingredient, whereas Blazer contains approximately 40% acifluorfen.

Acifluorfen has low acute oral, dermal and inhalation toxicity. It was not a skin sensitizer. However, it

caused severe eye and moderate skin irritation. Acute toxicity is shown in Table 1. The liver and kidney were target organs in subchronic and chronic studies with sodium acifluorfen. Anemia occurred in several studies.

Decreased body weight, liver toxicity (increased liver weight, microscopic liver lesions, elevated liver enzymes), and anemia occurred in the subchronic feeding studies in rats and mice. Increased kidney weights occurred in the subchronic rat study. Mortality, clinical signs, and dermal irritation occurred in the subchronic dermal toxicity study in rabbits. A toxicity profile is shown in Table 2.

Increased liver and kidney weights occurred in chronic rat, mouse, and dog studies and were accompanied by microscopic liver and kidney changes in the chronic rat and dog studies. Anemia was present in chronic rat and dog studies. Stomach ulcers were found in chronic rat and mouse studies. Testicular atrophy occurred in the chronic rat study. Increased mortality occurred in the high-dose group in rat and mouse studies.

Acifluorfen produced a statistically significant increase in the incidence of liver tumors (adenomas and carcinomas) and stomach tumors (papillomas) in mice. Tumors were not increased in the chronic rat study. The cancer classification is Group B2, probable human carcinogen, and the Q_1^* was 1.27×10^{-2} (mg/kg/day)⁻¹.

Acifluorfen is structurally related to other diphenyl ethers that have been shown to be oncogenic in rodents: lactofen, nitrofen, oxyfluorfen, and fomesafen. Nitrofen produced hepatocellular carcinomas in mice and pancreatic carcinomas in rats, oxyfluorfen produced marginally positive liver tumors in mice but was negative in rats, fomesafen produced hepatocellular adenomas and carcinomas in mice, and lactofen produced liver adenomas and carcinomas in mice and liver neoplastic nodules and foci of cellular alteration (possible precursor of tumors) in rats.

Acifluorfen was negative in several genetic toxicology studies but was weakly mutagenic in a bacterial reverse mutation assay when activated and was weakly recombinogenic in *Saccharomyces cerevisiae* when nonactivated. Because the significance of the positive bacterial assay data was not clear, it was recommended that sodium acifluorfen be retested in a modified bacterial assay. Three subsequent bacterial reverse mutation assays were negative.

Developmental toxicity in rats included increased resorptions, reduced fetal weights, slightly dilated lateral ventricles of the brain, hemorrhage in the eyeball, slight dilation of the renal pelvis, hemorrhage in peritoneal cavity and subcutaneous spaces, and changes in ossification. This study showed qualitative evidence of increased susceptibility of offspring because the developmental toxicity was accompanied by minimal maternal toxicity (excess salivation and piloerection). Developmental toxicity in rabbits with Blazer (39.8% a.i.) was shown by increased resorptions; accompanying maternal toxicity included clinical signs and severe mortality. No developmental or maternal toxicity occurred in a developmental study in rabbits with Tackle (22.4% a.i.) which used lower doses. The developmental studies in rabbits showed no evidence of increased susceptibility of offspring.

In a 2-generation reproduction study in rats, increased pup mortality and kidney lesions were seen in offspring; there were no changes in reproductive parameters. There was no indication of quantitative or qualitative susceptibility to offspring because offspring effects were observed only at or above treatment levels which resulted in evidence of parental toxicity.

The metabolism study showed that acifluorfen was rapidly absorbed orally and eliminated mainly in the urine (46-58% of the dose) and feces (21-41% of the dose). The major component present in urine and feces was unchanged acifluorfen and amine metabolite, respectively. No tissue accumulation was observed.

A dermal absorption value of 20% was determined by the Hazard Identification Assessment Review Committee (HIARC). In the dermal penetration study, 0.02% was absorbed 10 hours after treatment. However, 40% of the dose was still present on the skin and available for absorption after 10 hours. A dermal absorption value of 20% was determined by comparing oral and dermal rabbit toxicity studies (HIARC document 013308, 4/7/99).

Table 1. Acute Toxicity of Acifluorfen 2S (20.2% - 23.25% a.i.)

Guideline	Study Type	Results	Tox Category
81-1	Acute Oral (rats)	LD ₅₀ = 2025 mg/kg (males) LD ₅₀ = 1370 mg/kg (females)	III
81-1	Acute Oral (dog) ^a	LD ₅₀ = 186 mg/kg	II
81-2	Acute Dermal (rabbits)	LD ₅₀ > 2000 mg/kg (males/females)	III
81-3	Acute Inhalation	LC ₅₀ > 6.9 mg/L	IV
81-4	Primary Eye Irritation	An eye irritant	I
81-5	Primary Skin Irritation	Moderate dermal irritant	II
81-6	Dermal Sensitization	Not a skin sensitizer	

a: 40-70% a.i. (Blazer)

Table 2. Acifluorfen Toxicity Profile

STUDY TYPE – DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
Chronic/Carcinogenicity - Rat (1983) 0, 25, 150, 500, 2500, or 5000 ppm. (0, 1.25, 7.50, 25.0, 125, or 250 mg/kg/day based on 1 ppm=0.05 mg/kg/day). MRID No. 00128253; Accession No's. 071315 through 071317 and 250289 through 250792.	25	125 based on reduced body weight, increased absolute and relative liver weights and increased kidney weights, increased incidence of nephritis/pyelonephritis, increased incidence of acidophilic cells in the liver, and related changes in clinical chemistry parameters .
Carcinogenicity in Mice (1982). 0, 625, 1250, or 2500 ppm (males: 0, 119, 259, 655 mg/kg/day; females: 0, 143, 313, 711 mg/kg/day). MRID No. 00122732; Accession No's.071312, 071313, 071314, 250463, and 250464.	< 119	& #119 . & #143 based on reduced body weight, increased absolute and relative liver weights, and changes in hematologic parameters (decreased MCV counts, decreased segmented neutrophil counts, increased RBC counts, and increased lymphocyte counts).
Carcinogenicity in Mice (1979). 0, 7.5, 45, or 270 ppm (1.125, 6.75, or 40.5 mg/kg/day based on 1 ppm = 0.15 mg/kg/day) for 24 months. MRID No. 00082897.	6.75	40.5 based on increased absolute and relative liver weights, increased relative kidney weights, and increased levels of alkaline phosphatase and glutamic pyruvic transaminase activities.
2-Year Feeding Study in Dogs (1983). Tackle "2S" (purity unspecified). 0, 20, 300, or 4500 ppm (0, 0.5, 7.5 or 112.5 mg/kg/day based on 1 ppm = 0.025 mg/kg/day). MRID 00131162; Accession No's.251297, 251298.	7.5	112.5 based on decreased body weight gain, increased absolute and relative liver and kidney weights, changes in hematology, biochemistry, and urinalysis parameters and increased incidence of microscopic changes in the liver.
Subchronic Feeding Study in Rats (1982). 0, 20, 80, 320, 1250, 2500 or 5000 ppm (0, 2, 8, 32, 125, 250, or 500 mg/kg/day based on 1 ppm = 0.1 mg/kg/day). MRID No. 00122730; Accession No. 071308.	32	125 based on decreases in hematology parameters, increases in liver and kidney weights, and increased incidence of hypertrophy of liver cells when compared to the controls.
Subchronic Feeding Study in Mice (1982) 0, 20, 80, 320, 1250, or 2500 ppm (0, 3, 12, 48, 187.5 or 375 mg/kg/day based on 1 ppm = 0.15 mg/kg/day). MRID 00252826; Accession No. 071308.	48	187.5 based on histopathologic changes (fatty infiltration) of the liver.
4-Week Rangefinding Feeding Study in Mice (1983). (1983). 0, 59, 181, 522, 1286, 2471, 4983 ppm. MRID 45323503; Doc 014642.	27	78 based on increased absolute and relative liver weight and histological changes in liver.

STUDY TYPE – DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
Developmental Toxicity Study in Rats (1981) 0, 20, 90, or 180 mg/kg/day from gestation days 6 through 19. MRID No.00122743; Accession No. 071319.	Maternal: 20 Develop: 20	Maternal: 90 based on clinical signs (excessive salivation and piloerection). Developmental: 90 based on decreased fetal body weight and increase in anatomical variations.
Developmental Toxicity Study in Rabbits (1980) 0, 3, 12, or 36 mg/kg/day from gestation days 6 through 29. MRID No. 00122744; Accession No. 071319.	Maternal: \$ 36 Develop: \$36	Maternal: >36 Developmental: > 36
Developmental Toxicity Study in Rabbits (1979) 0, 20, 60, 180 mg/kg/day. MRID 00107485.	Maternal: 20 Develop: 60	Maternal: 60 based on clinical signs (anorexia, depression and dyspnea). Developmental: 180 based on fetal resorptions.
2-generation reproduction study in rats (1986) 0, 25, 500, or 2500 ppm (0, 1.25, 25, or 125 mg/kg/day based on 1 ppm = 0.05 mg/kg/day). MRID No.00155548.	Parental: 1.25 Repro: \$ 125 Offspring: 1.25	Parental: 25 based on kidney lesions, characterized predominantly by dilatation of tubules in the outer medulla, in females of both generations. Reproductive: > 125 Offspring: 25 based on decreased viability and increased incidence of kidney lesions, characterized predominantly by dilatation of pelvis in F2 generation.
21-day dermal toxicity study/rabbits (1981) 0, 100, 300, or 1000 mg/kg/day, for 6 hours/day and 5 days/week. MRID No. 00122731; Accession No. 071311.	Systemic: 300 Dermal irritat.: < 100	Systemic: 1000 based on mortality of 19/20 animals (both sexes) by day 8 of the study. Dermal irritat.: # 100

3.2 FQPA Considerations

The Health Effects Division (HED) FQPA Safety Factor Committee met on September 13, 1999 to evaluate the hazard and exposure data for acifluorfen. The FQPA Safety Factor Committee concluded that a safety factor is required because (1) there is qualitative evidence of increased susceptibility following *in utero* exposure to acifluorfen in the prenatal developmental toxicity study in rats (developmental toxicity was seen in the presence of minimal maternal toxicity at the same dose, see section 3.1 of this document); and (2) a developmental neurotoxicity study in rats is required for acifluorfen in order to further define the neurotoxic potential observed in the developing fetus in the prenatal developmental study in rats.

The FQPA Safety Factor Committee recommended that the FQPA safety factor for protection of infants and children (as required by FQPA) should be **retained at 10x** when assessing **acute dietary and short-/intermediate-term residential** (non-occupational) exposures for **Females 13-50**. The 10x safety factor was retained for these exposure scenarios because there was a qualitative increase in susceptibility in the rat developmental study and since there is a data gap for a developmental neurotoxicity study.

The FQPA safety factor should be **reduced to 3x** when assessing **chronic dietary and long-term residential (non-occupational) exposures** for **Females 13-50 and Infants and Children subgroups**. The safety factor was reduced to 3x because there is a data gap for the developmental neurotoxicity study. The qualitative increase in susceptibility seen after *in utero* exposure in the developmental study has no bearing on chronic exposure scenarios.

3.3 Dose Response Assessment

On January 19 and February 11, 1999, the Hazard Identification Assessment Review Committee (HIARC) evaluated the entire toxicological database on sodium acifluorfen and selected the relevant toxicity endpoints, taking into consideration the use patterns and exposure information on this chemical. The population adjusted dose (PAD) is equivalent to the Reference Dose (RfD) adjusted for the FQPA safety factor (see section 3.2 of this document for more details).

The selected toxicological endpoints and the doses for risk assessment are summarized in Table 3. The aPAD for dietary exposure for females 13-50 years of age is 0.02 mg/kg/day and is based upon decreased fetal body weights and an increased incidence of dilated lateral ventricles of the brain in a developmental rat study (NOAEL = 20 mg/kg/day). An aPAD was not selected for other populations because no other toxicity was observed which could be attributed to 1-day effects. The chronic PAD for the general population is 0.013 mg/kg/day based upon kidney lesions in both generations of a 2-generation reproduction study (NOAEL = 1.25 mg/kg/day). The chronic PAD (cPAD) for females 13-50, infants, or children is 0.004 mg/kg/day from the same study.

The endpoint for short- and intermediate term dermal or inhalation non-dietary exposure is the NOAEL from the developmental rat study based upon decreased fetal body weights and an increased incidence of dilated lateral ventricles of the brain. A 21-day dermal toxicity study in rats was not selected as an endpoint for dermal exposure because developmental effects which occurred in the rat developmental study were not determined in the 21-day dermal toxicity study. The Q^*_1 for carcinogenic effects is $5.30 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$ is based upon liver tumors and stomach tumors in a mouse carcinogenicity study.

TABLE 3. Doses and Toxicological Endpoints Selected for Various Exposure Scenarios

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (Female 13-50)	NOAEL=20 UF=100 FQPA SF=10	Decreased fetal weight and increased incidences of dilated lateral ventricles of the brain at 90 mg/kg/day	Developmental–rat
		Acute PAD = 0.02 mg/kg/day	
Acute Dietary (General population)	none	no endpoint established	
Chronic Dietary, non-cancer (General population)	NOAEL=1.25 UF=100 FQPA SF=3 (Females 13-50 and infants/ children)	Kidney lesions (dilatation of tubules in outer medulla) in females of both generations at 25 mg/kg/day	2-generation Reproduction–rat
		Chronic PAD = 0.013 mg/kg/day (general population) Chronic PAD = 0.004 mg/kg/day (infants, children, females 13-50)	
Carcinogenic effects	$Q^*_1 = 1.27 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$	liver tumors (adenomas, carcinomas, and adenomas/carcinomas combined) and stomach tumors (papillomas) in both sexes of mice	
^(a) Dermal (short and intermediate-term, females 13-50)	NOAEL=20 MOE=100 FQPA SF=10 (Females 13-50)	Decreased fetal weight and increased incidences of dilated lateral ventricles of the brain at 90 mg/kg/day	Developmental–rat
Dermal (long-term)	None	Based on registered uses, long term dermal exposure is not expected.	
^(b) Inhalation (short and intermediate-term, females 13-50)	NOAEL=20 MOE=100 FQPA SF=10 (Females 13-50)	Decreased fetal weight and increased incidences of dilated lateral ventricles of the brain at 90 mg/kg/day	Developmental–rat
Inhalation (long-term)	None	Based on registered uses, long term inhalation exposure is not expected.	

(a) = Since an oral NOAEL was selected, a dermal absorption factor of 20% of oral absorption should be used in route-to-route extrapolation.

(b) = Since an oral NOAEL was selected, an inhalation absorption factor of 100% of oral absorption (default value) should be used in route-to-route extrapolation.

3.4 Endocrine Disruption

The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) “may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect....” EPA has been working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency’s proposed Endocrine Disrupter Screening Program was published in the Federal Register of December 28, 1998 (63 FR71541). The Program uses a tiered approach and anticipates issuing a Priority List of chemicals and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of acifluorfen and its end-use products for endocrine effects may be required.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Sodium Acifluorfen (Sodium 5-[2-chloro-4-(trifluoromethyl) phenoxy] -2-nitrobenzoate; CAS # 62476-59-9) is the salt of a diphenyl ether and is used as contact herbicide. BASF has six active sodium acifluorfen end-use products (EPs; see Table A1) registered under FIFRA Section 3 for food/feed uses (EFS search conducted 3/6/00). There are two products for residential use (Sodium Acifluorfen Use Closure Memo, 11/01/99).

The agricultural products which are formulated as an emulsifiable concentrate (7 - 21% acifluorfen) are used for post emergence weed control in peanut, rice and soybean fields. The residential product (0.12% acifluorfen) is a ready to use trigger sprayer for spot treatments to kill weeds in driveways, sidewalks, patios and around trees.

As full coverage of a crop is required for acifluorfen to be effective as a contact herbicide, applications to peanuts, rice and soybeans are limited to the use of aerial and groundboom equipment. Several acifluorfen products contain other registered active ingredient pesticides, including bentazon, sodium salt; glyphosate, isopropylamine salt; and imazaquin, sodium salt. These active ingredients are not addressed in this risk assessment.

Based upon pesticide survey usage information for the years 1987-1997, the Biological and Economic Effects Division (BEAD) of EPA estimates that total annual domestic usage for applications of acifluorfen is approximately 1.5 million pounds active ingredient (ai) for about 6 million acres treated. Acifluorfen has its largest markets, in terms of total pounds active ingredient, allocated to soybeans (94%), peanuts (4%), and rice (2%). Most of this usage is in Arkansas, Mississippi, Illinois, Missouri, Indiana, North Carolina, Virginia, Texas and Alabama. Crops with a high percentage of the total U.S. planted acres treated include: soybeans (9%), peanuts (11%) and rice (4%).

Acifluorfen is not a significant plant metabolite of lactofen. Degradation of lactofen to acifluorfen in

water is approximately 52% and was included in the drinking water assessment. Exposure data to acifluorfen, as a degradate of lactofen, is not addressed in the occupational/residential exposure assessment.

4.2 Dietary Exposure and Risk

4.2.1 Dietary Exposure from Food

The reregistration requirements for plant metabolism are fulfilled. Acceptable metabolism studies were conducted on rice, peanuts, and soybeans for purposes of reregistration.

Adequate studies are available for depicting the metabolism in rice, peanuts, and soybeans. Major metabolites in crops included acifluorfen, acifluorfen amine and several conjugated metabolites. Tolerances for plant commodities are currently expressed in terms of the combined residues of sodium acifluorfen and its metabolites, including the corresponding acid, methyl ester, and amino analogues. Table 4 shows residues found in plants and animals.

Adequate studies are available for depicting the metabolism in ruminants and poultry. Major metabolites detected in ruminant tissues or milk included acifluorfen, acifluorfen amine, acifluorfen acetamide, and conjugates. Major metabolites in poultry included acifluorfen, acifluorfen acetamide, and descarboxy acifluorfen. Tolerances for animal commodities are currently expressed in terms of the combined residues of sodium acifluorfen and its metabolites, including the corresponding acid, methyl ester, and amino analogues.

The HED Metabolism Assessment Review Committee (MARC) met on 4/4/00 to discuss the residues of concern in food and water. The residues to be regulated and of toxicological concern in plants are those in the current tolerance expression, i.e., the parent compound (sodium salt; not expected to be present), acifluorfen acid, acifluorfen amine, and the methyl esters of the acid and the amine. The residues of concern to be used for the assessment of drinking water exposure and risk are acifluorfen and acifluorfen amine, the major soil/water residues. In consultation with the Chemistry Science Advisory Council, it was recommended that livestock tolerances be revoked because 40 CFR 180.6(a)(3) is applicable, i.e., there is no reasonable expectation of residues being transferred to livestock commodities via consumption of feed items derived from crops treated with sodium acifluorfen according to the current use directions. The Agency will reassess the need for additional residue characterization data in forage if registration is sought on crops having significant livestock forage raw agricultural commodities (RACs).

Adequate methods are available for enforcement of tolerances of acifluorfen in plant and animal commodities as currently expressed. The requirement for radiovalidation of the analytical methods are waived based on the low residues found in metabolism and field trial studies.

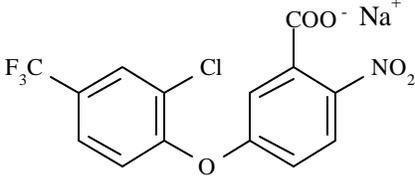
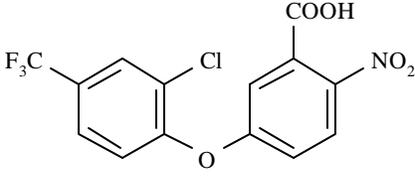
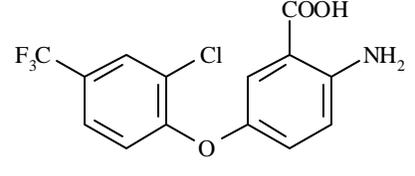
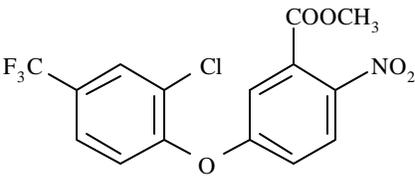
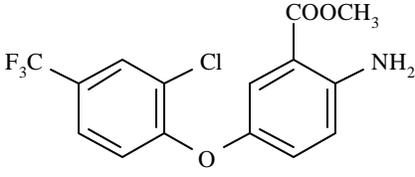
Except for the following requirements, the product and residue chemistry databases are complete. UV/visible absorption data (830.7050), and several labeling changes are the only outstanding requirements.

There is a tolerance for strawberries. Strawberries are currently not registered for use, but were included in this assessment because IR-4 has stated that it will support this use. For livestock commodities, a Category 3 situation under 40 CFR 180.6(a) exists with no expectation of finite residues and livestock tolerances should be revoked. Anticipated residues were based solely on field trial data. No monitoring data are available for sodium acifluorfen.

For the acute dietary exposure analysis, average field trial residues incorporating the likely maximum % crop treated (CT) were used as a point estimate for the blended commodities, rice, peanuts, and soybean. Although strawberries are considered to be partially blended, a point estimate equal to $\frac{1}{2}$ LOD was used in the assessment. Generally, for commodities which are considered to be partially blended or not blended, a distribution of field trial data incorporating zeroes to account for the percent crop not treated would be used in the assessment, however, since 100% crop treated and $\frac{1}{2}$ LOD was used for strawberries, there is no distribution of data.

Processing studies submitted by the registrant were used to generate anticipated residues for peanut, soybean and rice processed products. The data indicate that residues of acifluorfen and its metabolites do not concentrate in rice and peanut processed commodities and are reduced by 0.47X in soybean processed products.

Table 4. Chemical Names and Structures of Sodium Acifluorfen and its Regulated Metabolites.

<p>Common Name: Sodium acifluorfen</p> <p>Chemical Name: Sodium 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate</p> 
<p>Common Name: Acifluorfen</p> <p>Chemical Name: 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoic acid</p> 
<p>Common Name: Acifluorfen amine</p> <p>Chemical Name: 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-aminobenzoic acid</p> 
<p>Common Name: Acifluorfen methyl ester</p> <p>Chemical Name: Methyl 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate</p> 
<p>Common Name: Acifluorfen amine methyl ester</p> <p>Chemical Name: Methyl 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-aminobenzoate</p> 

4.2.2 Dietary Risk from Food

HED conducts dietary risk assessments using the Dietary Exposure Evaluation Model (DEEM™ Version 7.075), which incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For acute dietary risk assessments, the consumption distribution is multiplied by a residue point estimate for a deterministic exposure/risk assessment. For chronic dietary risk assessments, the three-day average of consumption for each sub-population is combined with average residues in commodities to determine average exposures in mg/kg/day. Table 6 shows Tier 1 and 3 dietary exposure and risks.

A dietary exposure less than the acute or chronic population adjusted dose (PAD) is not considered to be of concern. Food exposures and risks are shown in Tables 5 and 6. In the tier 3 dietary assessment, calculated acute and chronic dietary exposures were all less than 1% of the PAD and were not of concern. For dietary carcinogenic risk, the Agency's level of concern is 1×10^{-6} . Calculated dietary exposure resulted in a lifetime risk of 5.2×10^{-9} which is less than a level of concern.

Table 5. Summary of Acifluorfen Chronic Dietary Exposure and Risk Estimates.¹

Population Subgroup	Chronic Assessment				Cancer			
	Tier 1 ²		Tier 3 ³		Tier 1		Tier 3	
	Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	Lifetime Risk	Exposure (mg/kg/day)	Lifetime Risk
General US Population	0.000096	1	<0.000001	<1	0.000096	1.2 x 10 ⁻⁶	<0.000001	5.2 x 10 ⁻⁹
All infants (<1 year)	0.000419	10	0.000001	<1				
Children 1-6 years	0.000201	5	0.000001	<1				
Children 7-12 years	0.000136	3	0.000001	<1				
Females 13-50 years	0.00075	2	<0.000001	<1				

1 The chronic PAD (cPAD) is 0.004 for females 13-50 years, infants and children; 0.013 mg/kg/day for U.S. Population and all other subgroups.

2 The Tier 1 assessment included tolerance level residues and 100% crop treated.

3 The Tier 3 assessment include anticipated residues and % CT information provided by BEAD.

Table 6. Summary of Acifluorfen Acute Dietary Exposure and Risk Estimates.¹

Population Subgroup	Acute Assessment			
	Tier 1 ²		Tier 3 ³	
	95 th %-ile		99.9 th %-ile	
	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
Females 13-50 years	0.000289	1	0.000024	<1

1 The acute Population Adjusted Dose (aPAD) is 0.02 for females 13-50 years, no endpoint is established for the general population.

2 The Tier 1 assessment included tolerance level residues and 100% crop treated.

3 The Tier 3 assessment included anticipated residues and % CT information provided by BEAD.

4.2.3 Dietary Exposure from Water

This section reports potential exposures from the herbicide, sodium acifluorfen, and from acifluorfen as a metabolite of the herbicide, lactofen. (Memo, Drinking Water Exposure Assessment for Lactofen, Lactofen Derived Acifluorfen, and Acifluorfen-Sodium, D239268, James K. Wolf, Ph.D.; memo, Acifluorfen estimated drinking water concentrations (EDWC) for acifluorfen, 5/22/00; email, James Wolf, 5/22/00).

The HED Metabolism Assessment Review Committee determined that the residues of concern in drinking water are acifluorfen and acifluorfen amine, the major soil/water residues. The following Health Advisories have been established for acifluorfen per se by EPA's Office of Water: for children, 2 ppb for 1- and 10-day exposures and 0.1 ppb for long-term exposure; adults, 0.4 ppb for long-term; and cancer, 0.1 ppb at a 1/10,000 risk.

(a) Environmental Fate: Sodium acifluorfen is extremely water soluble, is stable to hydrolysis and is moderately persistent to persistent in soil and water. Aerobic soil metabolism half-lives ranged from 30 days up to 6 months; anaerobic soil metabolism half-life was less than 28 days. Acifluorfen is very mobile with low binding potential. In soil (pH > 3.5), acifluorfen is predominately an anion with little sorption in many soils. Acifluorfen binding increases with soil organic carbon content. Soil temperature and soil water content influence soil microbial activity and may influence acifluorfen's degradation rate. The decarboxy derivative of acifluorfen was the primary degradate found in solution. The amino analog of acifluorfen (amino acifluorfen) is the major degradate under anaerobic soil conditions. Depending upon soil type, amino acifluorfen ranged from immobile to medium mobility. The aerobic aquatic half-life was estimated to be 117 days.

In ground water, acifluorfen will be persistent due to its stability to abiotic hydrolysis. During runoff events, sodium acifluorfen may reach surface waters from ground water where it would also persist for some time (unless there is some photodegradation; <1 to 29 days half-life). Acifluorfen would not be expected to bioaccumulate in fish because of the low K_{ow} value.

(b) Monitoring Data: Monitoring studies have detected acifluorfen residues in ground and surface water. Because of uncertainties with the surface and ground water monitoring studies, monitoring data cannot be used in this risk assessment. It is generally not known whether detected acifluorfen is from application of acifluorfen or lactofen.

A small-scale prospective ground-water monitoring study was conducted for acifluorfen-sodium (known use) in a vulnerable area of Wisconsin. Acifluorfen was detected in 56 out of 283 samples with concentrations ranging from 1 to 46 : g/L. The study duration was from 4/20/88 to 4/12/89 and acifluorfen detections occurred from 9/14/88 through 4/12/89. The overall mean for the 56 detections was 8.36 : g/L. Because of the multiple detections, an understanding of the site's hydrology, and known sodium acifluorfen use, EFED is highly confident that acifluorfen residues can contaminate shallow ground water under vulnerable conditions. Although the wells sampled during the prospective study were not drinking water wells, people in the Central Sands region of Wisconsin where the study was conducted do use this type of shallow aquifer for drinking, if not contaminated. Amino acifluorfen was not detected in this study.

The Pesticides in Ground Water Database (PGWDB, USEPA, 1992) reported residues in 4 of 1185 wells sampled with concentrations ranging from 0.003 to 0.025 : g/L. The studies reported in PGWDB may reflect conditions where no lactofen or acifluorfen had been used or where there is a low susceptibility ground water contamination.

The only surface water monitoring for acifluorfen is that from the USGS National Water Quality Assessment (NAWQA). The NAWQA study reports a single acifluorfen detection of 0.17 : g/L out of 965 samples collected from major aquifers and 1 detection (0.07 : g/L) out of 314 samples collected from shallow urban ground water. There is uncertainty associated with this type of non-targeted survey monitoring, because the hydrology is not always well characterized, detailed pesticide use information is not always known, and the water is often sampled only once.

(c) Modeling: The Environmental Fate and Effects Division used PRZM/EXAMS and SCI-GROW modeling software to estimate acifluorfen concentrations in surface and ground water because uncertainties in the water monitoring data precluded their use in quantitative risk assessments.

There was considerable uncertainty in modeled acifluorfen concentrations obtained for surface water from PRZM/EXAMS and ground water from SCI-GROW models. More uncertainty was present in ground water modeling than with surface water modeling due to uncertainty with chemical fate parameters and rate of formation of acifluorfen from lactofen. Estimated environmental concentrations (EECs) are reported for acifluorfen concentrations from the herbicide, sodium acifluorfen, and as a degradate of the herbicide, lactofen.

The SCI-GROW screening model was used to estimate acifluorfen concentrations in ground water. The maximum acifluorfen concentration from the herbicide, sodium acifluorfen was 10.3 µg/L. Maximum concentration for acifluorfen as a degradate of lactofen was 5.4 µ/L.

The PRZM/EXAMS screening model was used to estimate acifluorfen concentrations in surface water. For sodium acifluorfen, maximum values were 14.0 µg/L for peak exposure (acute risk assessment), 3.0 µg/L for average annual exposure (chronic risk assessment), and 1.4 µg/l for multi-year mean exposure (cancer risk assessment). For acifluorfen as a degradate of lactofen, maximum values were

4.9 µg/L for peak exposure (acute risk assessment), 0.99 µg/L for average annual exposure (chronic risk assessment), and 0.34 µg/L for multi-year mean exposure (cancer risk assessment).

The surface water EECs were generated for the standard Mississippi cotton scenario using the concept of index reservoirs (IR) and the percent crop treated area (PCA = 0.20). The scenario represents 2 applications at the rate of 0.25 lb ai/A for the label's maximum total amount of 0.5 lb ai/A. at the Mississippi site for soybeans. PRZM and EXAMS input files were modified for the Index Reservoir. The PCA uses the Agency's soybean value of 0.41.

4.2.4 Dietary Risk from Water

Drinking water levels of comparison (DWLOCs) were calculated for use as a surrogate measure of exposure because uncertainties in the water monitoring data precluded their use in quantitative risk assessments. The DWLOCs were compared to the estimated environmental concentrations (EECs) modeled by SCI-GROW and PRZM/EXAMS as described above.

The $DWLOC_{acute}$ is the concentration in drinking water as a part of the aggregate acute exposure that occupies no more than 100% of the acute PAD. Similarly, the $DWLOC_{chronic}$ is the concentration in drinking water as a part of the aggregate chronic exposure that occupies no more than 100% of the chronic PAD. The $DWLOC_{cancer}$ is the concentration in drinking water as a part of the aggregate chronic exposure that results in a negligible cancer risk of 1×10^{-6} .

For acute drinking water assessments, contributions to risk include food and water exposures. Chronic assessments include food, water, and residential exposures, however, there are no chronic residential scenario for sodium acifluorfen.

There may be a concern if water exposure is greater than the DWLOC. The only scenario in which modeled water concentrations exceeded the DWLOC is for cancer risk: modeled concentrations for sodium acifluorfen in ground water (10.3 µg/l) and for acifluorfen as a lactofen degradate (5.4 µg/L) in ground water exceeded the DWLOC (2.8 µg/L). DWLOCs are shown in Tables 7, 8, and 9. In accordance with Office of Pesticide Programs policy (Steve Johnson, 11/17/97), if the estimated environmental concentrations exceed the DWLOCs, water monitoring data are required to refine the drinking water exposure estimate. The Special Review and Reregistration Division and the Environmental Fate and Effects Division determine the nature and extent of water monitoring required.

Table 7. DWLOCs for Chronic Exposure to Acifluorfen

Population Subgroup	Chronic PAD mg/kg/day	Food Exposure mg/kg/day	Target Max Water Exposure ¹ mg/kg/day	Ground Water Herbicide ³ Metabolite ⁴ µg/L	Surface Water Herbicide ⁵ Metabolite ⁶ µg/L	DWLOC ⁷ Chronic µg/L
Females 13-50	0.004	<0.000001	0.004	10.3 5.4	3.0 0.99	120
Children 1-6	0.004	0.000001	0.004	10.3 5.4	3.0 0.99	40
Infants < 1 yr	0.004	0.000001	0.004	10.3 5.4	3.0 0.99	40
General Population	0.013	<0.000001	0.013	10.3 5.4	3.0 0.99	455

Table 8. DWLOCs for Acute Exposure to Acifluorfen

Population Subgroup	Acute PAD mg/kg/day	Food Exposure mg/kg/day	Target Max Water Exposure ¹ mg/kg/day	Ground Water Herbicide ³ Metabolite ⁴ µg/L	Surface Water Herbicide ⁵ Metabolite ⁶ µg/L	DWLOC ⁷ Acute µg/L
Females 13-50	0.02	0.00002	0.02	10.3 5.4	14.0 4.9	600

Table 9. DWLOCs for Cancer Risk for Acifluorfen

Population Subgroup	Q ₁ [*]	Food Exposure mg/kg/day	Target Max Water Exposure ² mg/kg/day	Ground Water Herbicide ³ Metabolite ⁴ µg/L	Surface Water Herbicide ⁵ Metabolite ⁶ µg/L	DWLOC ⁷ Cancer µg/L
U.S. Population	1.27e-02	>0.000001	7.87e-05	10.3 5.4	1.4 0.34	2.8

1 Target Maximum Water Exposure (acute or chronic) = PAD - food exposure

2 Target Maximum Water Exposure (cancer) = $10^{-6}/Q_1^*$ - food exposure

3 Estimated environmental concentration for the herbicide, sodium acifluorfen, using SCI-GROW modeling

4 Estimated environmental concentration for acifluorfen as a degradate of the herbicide, lactofen, using SCI-GROW modeling, 52.3% conversion of lactofen to acifluorfen

5 Estimated environmental concentration for the herbicide, sodium acifluorfen, using PRZM/EXAMS modeling

6 Estimated environmental concentration for acifluorfen as a degradate of the herbicide, lactofen, using PRZM/EXAMS modeling

7 DWLOC = $\frac{\text{maximum water exposure (mg/kg/day)} \times \text{body weight (kg)}}{\text{water consumption (L/day)} \times 10^{-3} \text{ mg/}\mu\text{g}}$

body weight = 70 kg for adult males, 60 kg for adult females, 10 kg for children and infants

water consumption = 2 L/day for adult males and females, 1 L/day for children and infants

4.3 Occupational Exposure

There are concerns for two exposure scenarios (mixing/loading liquids for aerial application and mixing/loading liquids for groundboom application) at the baseline level, for non-carcinogenic risks and there are concerns for one exposure scenario (mixing/loading liquids for aerial application) at the baseline level, for carcinogenic risks. However, there are no concerns for either carcinogenic risk or non-carcinogenic risk to handlers when label-required PPE (personal protective equipment) or higher levels of mitigation are used. There are no concerns for post-application exposure to workers on day 0; the re-entry interval is 48 hours, based upon eye irritation. There are no concerns for residential uses or for residential post-application exposure.

4.3.1 Handler

HED has determined that private growers and custom applicators (i.e. mixers, loaders, applicators, flaggers) are likely to be exposed during acifluorfen use and that these uses would result in short/intermediate term exposures. Because the acifluorfen products are typically applied only one or two times per year, long-term or chronic exposures (i.e., daily exposures which occur for a minimum of several months) are not expected. The anticipated use patterns and current labeling indicate six exposure scenarios based upon the types of equipment that potentially can be used to make acifluorfen applications.

One chemical-specific exposure and biomonitoring study (MRID 423615-01) was submitted by BASF in support of the reregistration of acifluorfen. This study monitored the dermal exposure, inhalation exposure and urinary excretion of private grower owner mixer/loader/applicators who used Blazer for weed control in Wisconsin, New York and Maryland/Delaware. The blazer was applied to soybean fields at a rate of 0.50 lbs ai/acre using groundboom sprayers pulled by open cab tractors. The workers wore single layer PPE without respirators during mixing and baseline PPE during application. Dermal exposure was measured using 10 x 10 cm gauze patches, hand exposure was measured using bag washes, and inhalation exposure was measured in the breathing zone using personal air pumps with air sampling tubes. Biomonitoring was accomplished by measuring acifluorfen residues and metabolites in 24 hour urine samples collected by each test subject for several days before, during and after exposure.

This study was reviewed by the agency and parts of it were found to be acceptable. Most of the analytical dermal data was grade A or B except for the sun exposed dosimeter data which was rated grade C for low recovery. The inhalation data was rated as "low confidence" because the sampling tube did not include a component to capture the aerosol fraction of the herbicide spray. The urine data has severe limitations because the pharmacokinetics of acifluorfen was not well documented, many of the reported results were below the limit of quantification and there were only seven valid test subjects. For the above reasons, only the dermal and inhalation exposure data were used in this assessment. These data indicated that unit exposure values were 5 times higher than those predicted by the Pesticide Handlers Exposure Database (PHED), Version 1.1 (August 1998).

In addition to the submitted study, analyses for both private grower and custom applicator short/intermediate term exposures were performed using PHED. Five mixer/loader, applicator, mixer/loader/applicator and flagger scenarios were evaluated.

The submitted data and calculations indicate that the MOEs for two exposure scenarios (mixing/loading liquids for aerial application and mixing/loading liquids for groundboom application) are below 100 for the baseline level and exceed HED's level of concern. The MOEs for the remainder of the exposure scenarios are above 100 for baseline and higher levels of mitigation and therefore do not exceed HED's level of concern. The data input variables and calculations are included in Appendix B.

The cancer risk calculations for private grower and custom handler/applicator indicate that one exposure scenario (mixing/loading liquids for aerial application) exceeds 1.0×10^{-4} at the baseline level. All of the remaining exposure scenarios at the baseline and higher mitigation levels do not exceed 1.0×10^{-4} . None of the private grower scenarios exceed 1.0×10^{-6} at the label required PPE mitigation level. Approximately half of the custom applicator scenarios exceed 1.0×10^{-6} with label required and single layer PPE while only one scenario exceeds 1.0×10^{-6} with double layer PPE. None of the scenarios exceed 1.0×10^{-6} with engineering controls.

4.3.2 Post-application

The Agency has determined that workers may be exposed to acifluorfen during scouting, hand weeding and irrigating treated areas. Due to the frequency and duration of these exposures coupled with the dissipation of acifluorfen following applications, it was determined that these exposures would be short/intermediate term and would occur primarily by the dermal route. Inhalation exposures are not anticipated for post-application worker exposures, and the Agency currently has no policy/method for evaluating non-dietary ingestion by workers due to poor hygiene practices or smoking. As a result, only dermal exposures were evaluated in the post-application worker assessment. The Agency assumes that all harvesting of peanuts, rice and soybeans will be performed mechanically. In addition, the Agency assumes that transplanting by hand will not occur for these crops in the United States.

A study "Foliar Dislodgeable Residues of Blazer on Soybeans" (MRID 440911-01) was submitted by BASF in support of the reregistration of acifluorfen sodium. This study measured dislodgeable foliar residues (DFR) following groundboom application of Blazer to control weeds in soybean fields in Indiana, Mississippi and Georgia. Two applications, 15 days apart, were made at each site. The amount applied was 0.125 lb ai/acre for the first application and 0.375 lb ai/acre for the second application. Three samples at each site were collected before and after each application then 1, 3, 5, 7, 10, 14, 21, 28 and 35 days after the second application. Leaf disk samples were collected using leaf punches and were dislodged in an ivory soap solution. No acifluorfen sodium residue (LOQ = 0.012 $\mu\text{g}/\text{cm}^2$) was detected prior to either the first or second application at any of the sites. The average acifluorfen sodium DFR on day zero after the second application (n=3) ranged from 0.25 $\mu\text{g}/\text{cm}^2$ in GA to 0.74 $\mu\text{g}/\text{cm}^2$ in MS. Regression analysis of the LN of the DFR levels vs. the days after treatment yielded a half life of 1.4 days for the Indiana data ($r = 0.97$, n=18), 0.45 days for the Mississippi data

($r = 0.99$, $n=9$) and 0.72 days for the Georgia data ($r = 0.87$, $n= 9$).

The DFR study was reviewed by the Agency and was found to be acceptable. The DFR data for the Indiana and Mississippi sites were used for the calculations of Post Application exposures and risks. The Georgia data were not used because DAT 0 values were substantially less than the DAT 0 values for Indiana and Mississippi. The post application non-cancer risk calculations indicated that the MOEs were greater than 100 on Day 0 which suggests that the current REIs are appropriate. In addition, none of the post-application cancer risks to private grower and professional workers is greater than 1.0×10^{-4} for day 0 exposures at typical acifluorfen application rates. The current REI for acifluorfen is 48 hours based on acute eye irritation.

4.4 Residential Exposure

4.4.1 Handler

HED has determined that residential pesticide applicators are likely to be exposed to acifluorfen during one scenario (spot treat weeds in driveways, sidewalks, patios and around trees). Exposure data (MRID 444598-01) that had been submitted by Aventis in support of the reregistration of carbaryl was used to evaluate this scenario. This study, which included RTU trigger sprayer applications of an insecticide to home vegetable plants, was found to be of high quality and relevant to the acifluorfen exposure scenario. The calculations of residential applicators' non-cancer risks using study data indicated an MOE of 18000 which is greater than the target MOE of 1000 and is therefore not of concern. The target MOE of 1000 includes a 10X FQPA safety factor for females 13-50 years of age. A cancer risk of 4.5×10^{-8} was calculated for this scenario which is less than the target cancer risk of 1.0×10^{-6} and is therefore not of concern. There are no concerns of post application residential exposure because residential uses are limited to spot treatments which do not include broadcast application to lawns. In addition, the label states that acifluorfen kills grass.

4.4 Incident Reports

No incidents related to the use of sodium acifluorfen were reported from any of the data sources consulted by the Health Effects Division. Little or no usage has been reported for this pesticide, either in surveys of home use or agricultural use in California. On the list of the top 200 chemicals for which the National Pesticide Telecommunications Network received calls from 1984-1991, sodium acifluorfen was not reported to be involved in human incidents.

5.0 AGGREGATE RISK

An aggregate risk assessment, considering exposure from all non-occupational sources, including exposure from water, food, and residential use is required under the Food Quality Protection Act.

5.1 Acute Aggregate Risk

An acute aggregate exposure assessment includes only dietary (food and drinking water) exposure to acifluorfen. As reported in sections 4.2.3. and 4.2.4. of this document, drinking water levels of comparison (DWLOCs) were compared to modeling data because uncertainties in the water monitoring data precluded their use in quantitative risk assessments. The DWLOC_{acute} is the concentration in drinking water as a part of the aggregate acute exposure that occupies no more than 100% of the acute PAD. There may be a concern if modeled water exposure is greater than the DWLOC. As shown in Table 8, the modeled concentrations in surface and drinking water are much less than the DWLOC_{acute} and there is no concern for acute aggregate exposure.

5.2 Short-Term Aggregate Risk

A short-term aggregate risk assessment includes dietary (food and drinking water) and residential exposure (dermal, inhalation, and incidental oral) exposures. There are no incidental oral exposures for acifluorfen, due to its sole residential use as a spot weed treatment, and there was essentially no food exposure. The short-term aggregate assessment, therefore, included dermal and inhalation exposures and drinking water levels of comparison. A short-term aggregate risk assessment was calculated for the population subgroup of females 13-50 years only, because the margin of exposure is 1000x for this subpopulation and is 100x for the general population. The aggregate MOE was 4300 for this subpopulation, indicating that all population subgroups are protected. The short-term DWLOC for females 13-50 was 462 µg/L, which was far greater than the modeled water concentrations of 0.34-10.3 µg/L, indicating that there are no concerns for short-term aggregate exposure. See Table 10.

5.3 Intermediate-Term Aggregate Risk

Intermediate-term exposure is not expected for acifluorfen because residential uses are limited to spot treatments which do not include broadcast application to lawns (the label states that acifluorfen kills grass).

5.4 Chronic Aggregate Risk

A chronic aggregate exposure assessment includes food, drinking water, and residential exposure, however, no chronic residential exposure is anticipated for acifluorfen. As reported in sections 4.2.3. and 4.2.4. of this document, drinking water levels of comparison (DWLOCs) were compared to modeled water concentrations because uncertainties in the water monitoring data precluded their use in quantitative risk assessments. The DWLOC_{chronic} is the concentration in drinking water as a part of the aggregate chronic exposure that occupies no more than 100% of the chronic PAD.

There may be a concern if water exposure is greater than the DWLOC. As shown in Table 7, the modeled concentrations in surface and drinking water are much less than the DWLOC_{chronic} and there is no concern for chronic non-cancer aggregate exposure.

5.5 Aggregate Cancer Risk

The DWLOC_{cancer} is the concentration in drinking water as a part of the aggregate chronic exposure that results in a negligible cancer risk. The aggregate DWLOC for cancer was 2.6 µg/L (Table 11), compared to a DWLOC of 2.8 µ/L for cancer risk from water alone (Table 9). The difference in DWLOC values was due to dermal and inhalation exposure because the dietary contribution was essentially zero.

As shown in Table 11, the modeled concentrations for sodium acifluorfen in ground water (10.3 µg/l) and for acifluorfen as a lactofen degradate in ground water (5.4 µg/L) exceeded the DWLOC (2.6 µg/L). The modeled concentration from sodium acifluorfen in surface water (1.4 µg/L) also exceeded the DWLOC (2.8 µg/L).

In accordance with Office of Pesticide Programs policy (Steve Johnson, 11/17/97), if the estimated environmental concentrations exceed the DWLOCs, water monitoring data are required to refine the drinking water exposure estimate. The Special Review and Reregistration Division and the Environmental Fate and Effects Division should determine the nature and extent of water monitoring required.

Table 10. Aggregate Short-term Risk and DWLOCs for Acifluorfen

Population Subgroup	NOAEL mg/kg/day	MOE	Target Max Exposure ¹ mg/kg/day	Average Food Exposure mg/kg/day	Residential Exposure ³ mg/kg/day	Aggregate MOE ⁴ (food and residential)	Target Max Water Exposure ⁶ mg/kg/day	Ground Water: Herbicide ⁷ Metabolite ⁸ µg/L	Surface Water: Herbicide ⁹ Metabolite ¹⁰ µg/L	Short-term DWLOC ¹¹ µg/L
Females 13-50 years	20	1000	0.02	<0.000001	0.0046	4300	0.0154	10.3 5.4	1.4 0.34	462

Table 11. Aggregate Cancer Risk and DWLOCs for Acifluorfen

Population Subgroup	Q ₁ [*]	Negligible Risk	Target Max Exposure ² mg/kg/day	Food Exposure mg/kg/day	Residential Exposure (LADD) ³ mg/kg/day	Aggregate Cancer Risk ⁵ (food and residential)	Target Max Water Exposure ⁶ mg/kg/day	Ground Water: Herbicide ⁷ Metabolite ⁸ µg/L	Surface Water: Herbicide ⁹ Metabolite ¹⁰ µg/L	DWLOC ¹² Cancer µg/L
U.S. Population	1.27e-02	1.00e-06	7.87e-05	<0.000001	3.60e-06	4.5e-8	7.50e-05	10.3 5.4	1.4 0.34	2.6

1 Target Maximum Short-Term Exposure (mg/kg/day) = NOAEL/MOE.

2 Target Maximum Exposure for Cancer Risk (mg/kg/day) = negligible risk/Q₁^{*}

3 Residential Exposure Lifetime Average Daily Dose includes dermal and inhalation exposures

4 Aggregate MOE = NOAEL ÷ (Avg Food Exposure + Residential Exposure)

5 Aggregate Cancer Risk = Q₁^{*} x Exposure

6 Target Maximum Water Exposure (mg/kg/day) = Target Maximum Exposure - (Food Exposure + Residential Exposure)

7 Estimated environmental concentration for the herbicide, sodium acifluorfen, in ground water using SCI-GROW modeling

8 Estimated environmental concentration for acifluorfen as a degradate of the herbicide, lactofen, in ground water using SCI-GROW modeling, 52.3% conversion of lactofen to acifluorfen

9 Estimated environmental concentration for the herbicide, sodium acifluorfen, in surface water using PRZM/EXAMS modeling

10 Estimated environmental concentration for acifluorfen as a degradate of the herbicide, lactofen, in surface water using PRZM/EXAMS modeling

11 Short-Term DWLOC(µg/L) = $\frac{[\text{maximum water exposure (mg/kg/day)}] \times 60 \text{ kg body weight}}{2 \text{ L water consumption/day} \times 10^{-3} \text{ mg/}\mu\text{g}}$

12 Cancer DWLOC(µg/L) = $\frac{[\text{maximum water exposure (mg/kg/day)}] \times 70 \text{ kg body weight}}{(2 \text{ L water consumption/day}) \times 10^{-3} \text{ mg/}\mu\text{g}}$

6.0 CUMULATIVE RISK

Sodium acifluorfen is a member of the diphenyl ether group of herbicides, which includes lactofen and oxyfluorfen. In addition, acifluorfen is a degradate of lactofen. EPA has some evidence that these compounds induce similar toxic effects but has not yet determined whether or not these compounds exhibit a common mechanism. In addition, the Agency is in the process of developing methodology to conduct a cumulative risk assessment. For this assessment of acifluorfen, therefore, EPA will not conduct a cumulative risk assessment.

7.0 TOLERANCE REASSESSMENT RECOMMENDATIONS

Tolerances for residues in/on plant and animal commodities are established under 40 CFR §180.383. They are currently expressed in terms of the combined residues of the herbicide sodium salt of acifluorfen [sodium 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoic acid] and its metabolites (the corresponding acid, methyl ester, and amino analogues). The qualitative nature of the residue in plants and animals is adequately understood. HED has determined that the current tolerance expression for plant commodities is appropriate. As there is no reasonable expectation that residues will transfer from treated feed items to livestock tissues, HED recommends that livestock tolerances be revoked. See Table 11.

The chemical name for sodium acifluorfen listed in 40 CFR needs to be corrected; the correct name is "sodium 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate." In addition, at the time that the chemical name is corrected, the tolerance expression should be revised to specifically define the regulated metabolites.

Table 11. Tolerance Reassessment Summary for Sodium Acifluorfen.

Commodity	Current Tolerance, ppm	Reassessed Tolerance, ppm	Comment [Correct Commodity Definition]
Tolerances Established Under 40 CFR §180.383(a)			
Cattle, kidney	0.02	Revoke ¹	
Cattle, liver	0.02	Revoke	
Eggs	0.02	Revoke	[Egg]
Goats, kidney	0.02	Revoke	[Goat, kidney]
Goats, liver	0.02	Revoke	[Goat, liver]
Hogs, kidney	0.02	Revoke	[Hog, kidney]
Hogs, liver	0.02	Revoke	[Hog, liver]
Horses, kidney	0.02	Revoke	[Horse, kidney]
Horses, liver	0.02	Revoke	[Horse, liver]
Milk	0.02	Revoke	
Peanuts	0.1	0.1	[Peanut]
Poultry, fat	0.02	Revoke	
Poultry, mbyp	0.02	Revoke	
Poultry, meat	0.02	Revoke	
Rice grain	0.1	0.1	[Rice, grain]
Rice straw	0.1	0.2	Available data indicate maximum combined residues of sodium acifluorfen and metabolites were <0.124 ppm in/on rice straw. [Rice, straw]
Sheep, kidney	0.02	Revoke	
Sheep, liver	0.02	Revoke	
Soybeans	0.1	0.1	[Soybean, seed]
Strawberry	0.05	[0.05]	Use of sodium acifluorfen on strawberries is supported by IR-4. Currently there are no registered uses of sodium acifluorfen on strawberries. Tolerance reassessment cannot be finalized until there are approved use directions.
Tolerances Established Under 40 CFR §180.383(b)			
Cowpeas	0.1	Revoke	Expiration: 12/31/98. Extension of the expiration date for these tolerances has been denied (65 FR 3699, 1/24/2000)
Lima beans	0.1	Revoke	
Southern peas	0.1	Revoke	

¹Tolerances for residues of acifluorfen in livestock commodities should be revoked because it has been determined that there is no reasonable expectation that residues will transfer from treated feed items to livestock commodities.

7.1 Codex/International Harmonization

There are no Codex MRLs for sodium acifluorfen; therefore, there are no issues with respect to compatibility of Codex MRLs and U.S. tolerances.

8.0 DATA NEEDS

The Hazard Identification Assessment Review Committee recommended a developmental neurotoxicity study in rats be conducted (870.6300). This study is required because of neurotoxicity which occurred in a developmental toxicity study in rats (increased incidence of dilated lateral ventricles of the fetal brain, MRID 00122743).

The following product and residue chemistry requirements are needed. UV/visible absorption data (830.7050) and several labeling changes are the only outstanding requirements.

Several areas of the occupational and non-occupational risk assessment and characterization would improve with more information and data. Areas of information and data needs include:

- The agency requests additional dermal absorption data to refine the dermal absorption factor of 20% which was derived from a 1986 rat study. This study indicated that 1 to 43.5% of the applied dose remained on the skin following a ten hour exposure period and subsequent washing with distilled water.
- The agency requests additional pharmacokinetic data to interpret the biomonitoring study.

9.0 BIBLIOGRAPHY

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